In accordance with 37 C.F.R. § 1.12(c)(ii), a marked-up version of the amended claim is provided on a separate sheet at the end of this response under the heading of Marked-up Version of Claims.

REMARKS

Applicants respectfully request reconsideration of the present application.

I. Status of the Claims

Claims 1-48 remaining pending in this application, of which, claims 1-6, 9, 10 and 27 have been examined, pursuant to a restriction and election requirement.

II. Rejection of the Claims Under 35 U.S.C. § 112, second paragraph

Claims 10 and 27 were rejected as being indefinite under U.S.C. § 112, second paragraph. Claim 10 was held to be allegedly indefinite because "it is not clear how similar or dissimilar the other compounds must be to nalidixic acid, norfloxacin, ciprofloxacin or sparfloxacin and still be encompassed by this limitation." Office Action, page 3.

The Examiner also rejected claim 27 as being indefinite because "it is not clear how to determine how much licorice or dried root should be added to the composition." Office Action, page 3.

Applicants respectfully disagree and traverse these rejections.

A. The family of (fluoro)quinolones is well known to those in art

Applicants have amended claim 10 to remove the phrase "and similar compounds," because it is redundant. To clarify, compounds that would be

"similar" to those recited in claim 10 would fall within the scope of agents recited in claim 9. Accordingly, the amendment to claim 10 is not narrowing. For these reasons, Applicants respectfully request that this rejection be withdrawn.

B. An effective amount of licorice/dried root administered is taught in the instant application.

The Examiner alleges that claim 27 is indefinite because "it is not clear how to determine how much licorice or dried root should be added to the composition." Office Action, page 3.

Applicants assert that claim 27 recites that one gram of licorice contains the equivalent of 40 mg of glycyrrhizin. See the paragraph bridging pages 9 and 10 of the instant application for support.

The Examiner also is directed to page 17 of the specification that teaches the concentration of glycyrrhizin that is effective in enhancing the activity of certain antibiotics. There, Applicants state that "[I]n these experiments, the cancerous cells growth inhibition by Taxol (0.01μg/ml) in presence of glycyrrhizin (1μg/ml) was higher than even the treatment with Taxol (0.05μg/ml) alone."

Furthermore, Applicants emphasize that "in all the experiments the glycyrrhizin concentration was kept at 1 μg/ml, unless it is specifically mentioned" (page 14 of the instant specification).

In light of the preamble of claim 1, which recites "a composition comprising an effective amount of an extract or compound obtained from the plant *Glycyrrhiza glabra*", from which claim 27 depends, the skilled artisan would know how much licorice or dried root should be provided in order to administer "an effective amount" of glycyrrhizin.

Moreover, the instant application explicitly teaches what effect glycyrrhizin, at a concentration of 1 μg/ml, has upon the enhancement of antibiotics. See, for instance, Table 1 at page 14 of the specification where Applicants show the extent to which antibiotic activity is enhanced by glycyrrhizin. In fact, antibiotic activity may be enhanced anywhere from about 2 to 14 fold, depending on the concentration of antibiotic administered. For instance, Table 1 shows that administering the prescribed dose of glycyrrhizin to 2.0 μg/ml of tetracycline increases antibiotic activity by 1.9-fold in *E. coli*. Surprisingly, Applicants show that the effect of glycyrrhizin upon different antibiotic concentrations is not predictable since the relationship between "fold-enhancement" and antibiotic concentration is not linear. For example, Applicants show in Table 1 that administering the 1 μg/ml dose of glycyrrhizin to 4.0 μg/ml of tetracycline boosts antibiotic activity by 9-fold.

Applicants provide data on the activity of glycyrrhizin-enhanced antibiotics for a variety of other microorganisms, such as in *Bacillus subtilis* (Table 2, page 15), *Mycobacterium smegmatis* (Table 3, page 15) and *Candida albicans* (page 15, Table 4, page 16).

Accordingly, there is sufficient support, guidance and teaching in the instant specification that would allow the skilled artisan to precisely determine how much licorice or dried root should be added to the composition in order to enhance the activity of a combined antibiotic.

Applicants, therefore, respectfully submit that the Examiner's rejections under 112, second paragraph should be withdrawn.

III. Rejection of the Claims Under 35 U.S.C. § 102(b)

Claims 1-5 and 27 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,939,050. Claims 1-6 and 27 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,770,217.

A. The Examiner's Basis for the Rejections

The Examiner rejected claims 1-5 and 27 as being anticipated by U.S. Patent No. 5,939,050 because "US '050 allegedly teaches an anti-microbial composition that contains *G. glabra* extract and other anti-microbial agents. The *G. glabra* extract contains glycyrrihizic acid." Office Action, page 3.

The Examiner rejected claims 1-6 and 27 as anticipated by the '217 patent which allegedly "teaches a composition that contains *G. glabra* and other herbal ingredients." Office Action, page 4.

B. The claims are not anticipated by U.S. Patents 5,939,050 and 5,770,217

Claims 1-6 and 27 are not anticipated by either the '050 patent or the '217 patent. Claim 1, at page 25 of the instant application, recites a composition comprising "an effective amount of an extract or compound obtained from the plant *Glycyrrhiza glabra* and useful as a bio-enhancer and bioavailability facilitator" (emphasis added). Neither the '050 patent nor the '217 patent teaches these limitations. The alleged prior art does not teach a composition which uses *Glycyrrhiza glabra* as a bio-enhancer and bioavailability facilitator.

The present invention deals with enhancing the activity of antibiotics, vitamins, anti-cancerous compounds using glycyrrhizin at a concentration at which it has negligible antibiotic or antibacterial properties of its own.

Furthermore, neither patent teaches that one gram of licorice or dried root is equivalent to 40 mg of glycyrrhizin. Accordingly, claim 27 is not anticipated.

IV. Rejection of the Claims Under 35 U.S.C. § 103

Claims 1, 6 and 27 were rejected as unpatentable over U.S. Patent No. 5,770,217. Claims 1, 5, 6, 9, 10 and 27 were rejected as being unpatentable over U.S. Patent No. 5,939,050, The Merck Index and U.S. Patent No. 5,478,829.

A. The Examiner's Basis for the Rejections

The Examiner rejected claims 1, 6 and 27 as unpatentable over U.S. Patent No. 5,770,217, because the '217 patent allegedly teaches "administering *G. glabra* extract in combination with antibacterial agents." The '217 patent teaches a blend of 12 herbs or herbal extracts including *G. glabra* which modulates hematological toxicity, enhances the immune system and maintains appetite and weight.

The Examiner makes the erroneous assumption that "the amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize," yet admits that the '217 patent "does not specifically teach adding *G. glabra* in the full range of amounts claimed by applicant" (Office Action, pages 4 and 5).

The Examiner also alleges that the '050 patent teaches that *G. glabra* "is an anti-bacterial agent," that The Merck Index teaches "nalidixic acid, norfloxacin and ciprofloxacin are anti-bacterial agents" and that the '829 patent teaches "sparfloxacin is an anti-bacterial agent." Applicants disagree with this allegation and traverse the rejection.

B. The claims are not obvious under U.S. Patent 5,770,217

After reading the '217 patent, one of ordinary skill in the art would not arrive at Applicants' claimed composition because the '217 patent teaches concentrations at which *G. glabra* possesses antibacterial properties.

By contrast, the instant invention teaches concentrations at which *G. glabra* has negligible antimicrobial or antibacterial properties. In fact, it was Applicants' surprising discovery that, when used at low concentrations, *G. glabra* actually enhances the activity of the compounds with which it is combined, as well as improves the bioavailability of associated compounds to target sites. "The main object of the invention is to provide novel compositions comprising extracts and compounds from the plant *Glycyrrhiza glabra* useful as a bioenhancer and capable of improving or enhancing the bio-availability of drugs such as antibiotics, anti-infective agents and of nutritional compounds" (see page 4 of the instant specification). Other objects of the invention include the use of *G. glabra* to enable "effective transport of drugs and molecules across biological membranes to reach target sites," (see page 5, first paragraph of the specification) and to use *G. glabra* to enhance "the bio-availability of drugs, molecules and nutritional [compounds] to the target site in the body" (see page 5, paragraph 2 of the specification).

Accordingly, the instant invention does not envision the use of *G. glabra* as an antibacterial or antiviral agent. In contrast, the '217 patent does predict the usage of *G. glabra* to "stimulate T-cell activity and interferon production and to reduce inflammation and fatigue" (column 5, lines 49-50). The patent holder states that *G. glabra* also is useful because it exhibits "significant antiviral activity" (column 5, line 54). Thus, the *G. glabra* of the '217 patent is not used to enhance the properties of the substances with which it combined, but rather to contribute directly to stimulating the immune system.

The '217 patent teaches the combination of compounds, each of which can stimulate the body's immune system. The '217 patent does not teach combining a compound that can induce an immune response with a compound that does not stimulate the immune system.

For these reasons, the skilled artisan would not be motivated to use the '217 patent to "determine the optimal amount of each ingredient to add in order to best achieve the desired results" (Office Action, page 5), because the "optimal amount" of *G. glabra* is one which directly stimulates the immune system. It would not be obvious to add an amount of *G. glabra* disclosed in the instant invention, because such an amount would render *G. glabra* with negligible immunoreactivity. Conversely, it would not be obvious to use an amount of *G. glabra* disclosed in the '217 patent because such an amount makes the *G. glabra* capable of stimulating the immune system. Thus, the "optimal amount" of *G. glabra* used in the instant invention is to enhance the bioactivity of other compounds.

The Examiner implies that a "demonstration of unexpected results," would render such optimization as non-obvious; "[A]bsent some demonstration of unexpected results ... this optimization of ingredient amount would have been obvious," Office Action, page 5). By the same token, Applicants' unexpected finding that *G. glabra* can be added at a concentration which enhances the bioactive properties of substances with which it is combined, proves that optimization would not have been obvious at the time of Applicants' invention.

See, for instance, Tables 1-4 at pages 14-16 of the specification which illustrate the enhancing and bioavailability-facilitating properties that 1 μg/ml of glycyrrhizin has upon a range of antibiotics and their ability to kill various pathogens.

C. The claims ar not obvious over U.S. '050, The Merck Index and U.S. '829

The Examiner believes that the combination of U.S. '050, The Merck Index and U.S. '829 renders Applicants' invention obvious. The Examiner's assumption is wrong, because the Examiner has failed to appreciate the concept of the instant invention.

The Examiner states that "no patentable invention resides in combining old ingredients of known properties," (Office Action, page 6). Applicants state that while glycyrrhizin is an "old ingredient" its use as a bioenhancer and bioavailability-facilitator was not a known property. It was Applicants' surprising discovery that, at low enough concentrations, glycyrrhizin actually enhanced the activity of compounds with which it was associated.

Applicants respectfully reemphasize that, contrary to the Examiner's assertions, the *G. glabra* of the instant invention is not used as an antibacterial agent. The '050 patent claims a composition that contains two antimicrobial agents A and B wherein, agent A may be *Glycyrrhiza glabra* extract. See column 5, lines 49-63 of the '050 patent. The Examiner purports that "it is well known that it is *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose." Office Action, page 5.

Applicants, however, do not combine two or more ingredients each of which has antibacterial properties to create a third composition. The *G. glabra* extract used does not have the same properties as the biological agents with which it is combined.

Neither The Merck Index nor the '829 patent teach or suggest the use of a *G. glabra* extract or compound as a bioenhancer or bioavailability facilitator. The person of ordinary skill in the art, after reading these documents, would misleadingly use greater quantities of *G. glabra* extract than that which is required for the instant invention and, therefore, would not enhance the bioactivity of associated agents.

The Examiner states "the references do not specifically teach adding the *G. glabra* extract in the amounts claimed by applicant" (Office Action, page 6). Applicants affirm that the amount of *G. glabra* extract used is critical to practice the claimed invention, because it is only at "the amounts claimed by applicant" that *G. glabra* possesses bioenhancing and bioavailability facilitating properties.

The Examiner's admission that none of the references teach such an amount of *G. glabra* qualifies the instant invention as non-obvious over the cited art. Accordingly, Applicants respectfully request that these rejections be withdrawn.

V. Conclusion

It is respectfully urged that the examined claims are now in condition for allowance. Favorable reconsideration of the generic claims and the remaining elected claims is respectfully requested. Further, it is respectfully urged that, upon allowance of the elected claims, non-elected claims 28-48 should be rejoined under the *Ochiai* guidelines, as noted in Applicants' response to the restriction requirement.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date: October 1, 2001

Bernhard D. Saxe
Reg. No. 28,665

Foley & Lardner
Washington Harbour
3000 K Street, NW, Suite 500
Washington, DC 20007-8696
(202) 672-5300

MARKED-UP VERSION

10. (Once amended) A composition as claimed in claim 9 wherein the quinolones and fluoro-quinolones are selected from the group consisting of nalidixic acid, norfloxacin, ciprofloxacin and sparfloxacin [and similar other compounds].